REMARKS

Applicant respectfully requests reconsideration. Claims 1, 3-6, 10-12, 20 and 21 were previously pending in this application. Claims 10-12 are withdrawn. New claims 22 and 23 have been added. Claim 22 is supported throughout the specification and claims as filed and in particular by claim 1. Claim 23 is supported throughout the specification and in particular on page 12, lines 20-23 of the application as filed (i.e., the published PCT application). No new matter has been added.

As a result, claims 1, 3-6, 10-12 and 20-23 are pending for examination with claim 1 being an independent claim and claims 10-12 being withdrawn.

Interview Request

Applicant respectfully requests a personal interview with the Examiner at the Patent and Trademark Office at a mutually convenient time in the event that this amendment does not place all claims in condition for allowance.

Rejections Under 35 U.S.C. § 103

1. *Rejection over Lorincz (WO 99/29890 A2)*

The Examiner rejected claims 1-9 and 13-20 under 35 U.S.C. § 103(a) as being unpatentable over Lorincz (WO 99/29890 A2). Applicant respectfully traverses the rejection.

In response, Applicant maintains that Lorincz does not teach classification of subjects as "high risk" or "no detectable risk" for development of cervical carcinoma based purely on a

yes/no determination for expression of E6 mRNA transcripts from one of HPV types 16, 18, 31, 33 or 45.

The Examiner has highlighted a passage on page 8 that is asserted to teach that the level of expression of one HPV gene selected from E6, E7, L1 and E2 can be indicative of the stage of HPV-based disease. In fact, the passage on page 8, lines 10-12 simply states, in general terms, that "the level of expression of these genes [i.e. HPV E6, E7, L1 *and* E2 genes], the ratio of expression of these genes to each other or to one or more or to one or more other genes, or both, are indicative of the stage of HPV-based disease". This passage fails to make a clear specific link between expression levels of any one of the genes E6, E7, L1 or E2 and any specific stage of HPV-based disease. More particularly, this passage does not disclose a specific relationship between expression of HPV E6 mRNA and *high risk* for development of cervical carcinoma.

The sentence spanning lines 10-12 on page 8 of Lorincz would not be read and understood by a skilled reader in isolation from the remainder of the paragraph spanning lines 5-24. When one reads this passage a whole, the following sentence at lines 13-15 on page 8 confirms that "the level of expression is relative to other HPV genes or the level of expression relative to a non-HPV gene". Thus, reading the whole passage on page 8 lines 5-15, Lorincz again teaches that quantitative determination of expression levels is essential, and that expression levels must be measured relative to another HPV gene or a non-HPV gene. It should also be noted that this passage does not explicitly refer to expression of mRNA transcripts, it simply refers to the "level of gene expression".

To conclude, the passage on page 8 referred to by the Examiner does not teach or suggest classification of subjects "high risk" or "no detectable risk" for development of cervical carcinoma based purely on a yes/no determination for expression of E6 mRNA transcripts. The teaching in Lorincz would not give the skilled person a reason to measure expression of any particular gene, let alone E6 specifically, and to use the presence of the expression of E6 to classify a person as high risk for development of cervical carcinoma. Indeed, there is nothing

disclosed in Lorincz that would give to the skilled person a reasonable expectation of success in making the claimed invention.

The Examiner again acknowledges on page 4 of the Office Action that "Lorincz does not expressly teach categorizing people as "high risk" based on expression results". However, the Examiner considers that Lorincz must "clearly suggest" such a method step, because the disclosure makes specific reference to expression levels of HPV oncoproteins encoded by HPV strains 16 and 18 being associated with malignant cancer.

In response, Applicant submits that any statements regarding expression levels of HPV oncoproteins are irrelevant to the claimed method, which is expressly based on detection of E6 mRNA transcripts. A person skilled in the art of HPV biology would be able to inform the Examiner that levels of E6/E7 oncoprotein expression do not necessarily correlate with steady state levels of E6 mRNA transcripts. Thus, statements regarding expression of E6 or E7 oncoproteins would not suggest to a skilled reader that patients can be classified based on E6 mRNA expression.

As discussed in Applicant's previous response, Lorincz *expressly* teaches that individuals can be classified according to the stage of HPV-based disease based on mRNA expression, but Lorincz teaches that this classification should be based on relative expression levels of two or more HPV mRNA transcripts. More specifically, the method of Lorincz classifies patients on the basis of a calculated ratio between the levels of expression of mRNA transcripts of the E6 and/or E7 genes and the levels of expression of mRNA transcripts from the E2 and/or L1 genes. The method of Lorincz thus requires accurate quantitation of expression levels of at least two genes, and the calculation of a numeric ratio between the expression levels in order to assess the stage of HPV-based disease (see Summary of the Invention on page 4, lines 20-24 and claims 1-5).

Therefore, Lorincz fails to teach or suggest that subjects can be classified as "high risk" or "no detectable risk" for development of cervical carcinoma based purely on a yes/no

determination for expression of E6 mRNA transcripts from one of HPV types 16, 18, 31, 33 and 45 as is claimed by Applicant.

Applicant's previous response was not fully persuasive to the Examiner for the reasons set out on pages 5 and 6 of the Office Action, to which Applicant wishes to respond. Firstly, the Examiner is of the opinion that claim 1 does not exclude detection of another gene and calculation of the numeric ratio between expression levels because the claim is recited in open-ended "comprising" language. Applicant must strongly disagree with the Examiner's interpretation. Claim 1 expressly requires that subjects are sorted into one of two categories of risk for development of cervical carcinoma based on expression of E6 mRNA, with subjects positive for E6 mRNA classified as "high risk" and subjects negative for E6 mRNA being classified as "no detectable risk". Despite the "comprising" language, claim 1 does not encompass any method which *lacks* this feature. Hence, claim 1 does not encompass the method of Lorincz wherein individuals are classified based on a ratio between expression of levels of mRNA transcripts of the E6 and/or E7 genes and mRNA transcripts from the E2 and/or L1 genes, because Lorincz does not teach that subjects positive for E6 mRNA are classified as high risk and subjects negative for E6 mRNA are classified as no detectable risk.

Applicant has added new claim 23, which recites the additional patentable feature that the subjects are sorted into one of two categories of risk for development of cervical carcinoma based on expression of E6 *alone*.

The Examiner also maintains that the "ratio" teaching of Lorincz is only one embodiment and that Lorincz teaches alternative methods which do not require quantitation of transcripts and calculation of a numeric ratio. In this regard, the Examiner again cites the passage on page 8, lines 10-12 of Lorincz. In response, Applicant again submits that Lorincz does *not* teach a method having all features of current claim 1, in which subjects are sorted into risk categories based only on expression of E6 mRNA transcripts.

The Examiner has now twice acknowledged in separate Office Actions that "Lorincz does not expressly teach categorizing people as 'high risk' based on expression results". Moreover, as discussed previously, the passage on page 8, lines 10-12 simply states, in general terms, that "the level of expression of these genes [i.e. HPV E6, E7, L1 *and* E2 genes], the ratio of expression of these genes to each other or to one or more or to one or more other genes, or both, are indicative of the stage of HPV-based disease". This passage fails to make any clear links between expression levels of any one of the genes E6, E7, L1 or E2 and any specific stage of HPV-based disease. Accordingly, a person of ordinary skill in the art is not able to derive a specific relationship between expression of HPV E6 mRNA and *high risk* for development of cervical carcinoma from this general disclosure.

Claim 1 as presented recites detection of E6 mRNA from HPV types 16, 18, 31, 33 *and/or* 45, which necessarily includes as one embodiment detection of E6 mRNA from each of HPV types 16, 18, 31, 33 and 45. Applicant has added a new claim (claim 22) to recite separately this embodiment. Claim 22 thus requires that the subject be screened for E6 mRNA from each of types 16, 18, 31, 33 and 45, and classified as high risk if positive for E6 mRNA from (at least) one of these HPV types.

Lorincz does not disclose a method based on detection of E6 mRNA expression from each of HPV types 16, 18, 31, 33 *and* 45. Lorincz mentions only HPV types 16 and 18. Therefore, claim 22 is distinct from Lorincz.

Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as being unpatentable over Lorincz is respectfully requested.

2. *Rejection over Lorincz in combination with Hendricks (US 5,580,970)*

The Examiner rejected claims 21 under 35 U.S.C. § 103(a) as being unpatentable over Lorincz (WO 99/29890 A2) and US 5,580,970 (Hendricks). Applicant respectfully traverses the rejection.

The failure of Lorincz to teach certain features of the claimed invention is discussed above.

The Examiner states that Hendricks demonstrates that it was known in the art that HPV 52 is associated with cervical neoplasia and that it therefore would have been obvious to screen human subjects for the expression of E6 from HPV 52 in addition to HPV 16.

Hendricks lists HPV 52 as a "high risk" HPV type and states, in the Summary of the Invention at column 1, lines 60-66, that an embodiment of the invention involves using nucleic acid probes which hybridize to transcripts of the E6 and/or E7 genes of HPV types, including type 52. However, this passage provides no guidance as to how the probes are to be used to assess risk of developing cervical carcinoma. This passage does not disclose a screening method wherein in subjects are classified as "high risk" or "no detectable risk" for development of cervical carcinoma basely solely on a yes/no determination of expression of E6 mRNA transcripts from HPV type 52 as is claimed by Applicant.

Thus Hendricks does not supply the features of the claimed invention that are missing from Lorincz. The combination of references cited by the Examiner does not supply the elements of the claimed invention.

Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as being unpatentable over Lorincz and Hendricks is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: February 15, 2008

Respectfully submitted,

By: _____

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